UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/540,402	06/30/2006	Yoram Groner	85189-12200	8368

28765 7590 09/02/2008

WINSTON & STRAWN LLP
PATENT DEPARTMENT
1700 K STREET, N.W.
WASHINGTON, DC 20006

EXAMINER	
SGAGIAS, MAGDALENE K	
ART UNIT	PAPER NUMBER
1632	

MAIL DATE	DELIVERY MODE
09/02/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/540,402	GRONER ET AL.	
	Examiner	Art Unit	
	MAGDALENE K. SGAGIAS	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 June 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,9,13 and 49-53* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,9,13 and 49-53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's arguments filed 6/16/08 have been fully considered but they are not persuasive. The amendment has been entered. Claims 1-7, 9, 13, 49-53 are pending and under consideration. Claims 8, 10-12, 14-48 are canceled.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-7, 9, 13, 49-53 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 1-7, 9, are directed to an ex vivo method for up regulating runt-related transcription factor3 (RUNX3) expression in a subject, comprising: delivering an active agent to immune cells of said subject having low activity or no activity of RUNX3 gene product: wherein said active agent induces in vitro expression or over-expression of RUNX3 in said immune cells of said subject and administering back said in vitro-expressed or -over-expressed RU2NX3 stem cells to said subject, thereby inhibiting the proliferation of T-cells in said subject. Embodiments limit the immune cells to thymocytes and dendritic cells (DC). Independent claim 13 is directed to an ex vivo method for reducing the proportion of mature dendritic cells versus immature dendritic cells in a subject, comprising: delivering an active agent to immune cells of said subject having low activity or no activity of runt-related transcription 3 factor (RUNX3) gene

product, wherein said active agent induces in vitro expression or over-expression of RUNX3 in said immune cells of said subject and administering back said in vitro-expressed or -over-expressed RUNX3 stem cells to said subject, thereby reducing the proportion of mature dendritic cells versus immature dendritic cells in said subject.

The specification teaches LPS or DC maturation-inducing-reagents induced maturation of WT DC, reflected in elevated surface expression levels of MHC II and CD86 (FIG. 6B, C). This LPS induced maturation was significantly more pronounced in the KO DC (FIG. 6B, C). The specification also teaches RUNX3 KO DC were significantly more efficient stimulators of CD4+ T-cell proliferation compared to WT DC (FIG. 6E) [00141]. However, the specification fails to provide sufficient guidance to correlate the ability of LPS to induce maturation of knock out DCs or the ability of WT and KO DC that stimulate T cells in vitro to **a)** upregulate RUNX3 in a subject by delivering an active agent to immune cells of said subject having low activity or no activity of RUNX3 gene product: wherein said active agent induces in vitro expression or over-expression of RUNX3 in said immune cells of said subject and administering back said in vitro-expressed or -over-expressed RU2NX3 stem cells to said subject, thereby inhibiting the proliferation of T-cells in said subject and **b)** reducing the proportion of mature to immature DCs in a subject by delivering an active agent to immune cells of said subject having low activity or no activity of runt-related transcription 3 factor (RUNX3) gene product, wherein said active agent induces in vitro expression or over-expression of RUNX3 in said immune cells of said subject and administering back said in vitro-expressed or -over-expressed RUNX3 stem cells to said subject, thereby reducing. Thus, as enablement requires the specification to teach how to make and use the claimed invention, the specification fails to enable the claimed methods for upregulating RUNX3 expression or reducing the proportion of mature to immature DCs in a

subject by way of the claimed methods. It would have required undue experimentation to make and use the claimed invention without a reasonable expectation of success.

As a first issue the claims embrace delivering an active agent to immune cells of a subject in vitro having low or no activity of RUNX3 resulting in overexpression of RUNX3 in said cells and readministering into the subject said in vitro-expressed or over-expressed stem cells resulting in the inhibition of proliferation of T cells in the subject. The specification teaches agents such as LPS, TNF alpha and anti CD40 antibodies as efficient stimulators CD4+ T-cell proliferation of RUNX3 knock out dendritic cells compared to WT dendritic cells in vitro [0140] [0141]. The specification further contemplates compositions for inhibiting T cell-mediated inflammation comprising as an active ingredient an agent that induces up-regulation of RUNX3 expression in cells [0021]. The specification contemplates compositions for inhibiting T cell-mediated inflammation are useful in situations where it is desirable to down-modulate an immune response, for example in a transplant patient or a subject suffering from an autoimmune disease including but not limited to systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) and other forms of arthritis, multiple sclerosis (MS), ulcerative colitis, Crohn's disease, pancreatitis, diabetes, psoriasis, or other disorders associated with an abnormal immune response [0021].

At the time of filing the art taught that delivering an active agent to any type of immune cells from a subject in vitro, resulting in overexpressed RUNX3 stem cells and administering back to the subject resulting in inhibiting proliferation of T cells of the subject in vivo is unpredictable without undue experimentation. The claims embrace any type of immune cells for overexpression of RUNX3 in vitro and inhibiting proliferation of T cells in vivo. **David-Fung et al,** (Immunological Reviews, 209: 212–236, 2006) note fetal pro-T-cell specification process is shown to deploy a highly distinctive balance of potent regulators that should make it work

differently from the adult process in several respects. One can only speculate at this point about the consequences of these differences (p 231, 1ST column). David-Fung et al, note Runx3 is expressed differentially between fetus and adult implicated in proliferation (p 231, 1ST column). **Coffman** (Cell Biology International, 27: 315-324, 2003 (IDS) notes in mammals, Runx proteins are protooncogenes and tumor suppressors and the role of RUNX3 in cell proliferation is unclear (P 321, 1ST paragraph). Coffman notes that independent studies from two different labs have demonstrated that *Runx3* knockout mice manifest severe limb ataxia due to defective development of proprioceptive neurons in the dorsal root ganglia (p 318, 1st column, last paragraph). In another study *Runx3* knock out mice displayed hyperproliferation and suppressed apoptosis of epithelial cells in the gastric mucosa, and died shortly after birth apparently due to starvation (p 318, 1st column, last paragraph). However, this phenotype was not found in the *Runx3* knockout mice produced by Levanon et al in 2002, (Coffman, p 318, 1st column, last paragraph). The reason for the discrepancy between the different *Runx3* knockout phenotypes is not clear (p 318, 1st column, last paragraph). As such the art teaches that the role of RUNX3 in all types of immune cells is not clear even after the filing of the instant application.

As a second issue, claim 13 and its dependent claims embrace reducing the proportion of mature to immature DCs in vivo by delivering an active agent to immune cells of said subject having low activity or no activity of runt-related transcription 3 factor (RUNX3) gene product, wherein said active agent induces in vitro expression or over-expression of RUNX3 in said immune cells of said subject and administering back said in vitro-expressed or -over-expressed RUNX3 stem cells to said subject, thereby reducing the proportion of mature dendritic cells versus immature dendritic cells in said subject. The specification teaches increased ratio of mature to immature dendritic cells, in the RUNX3 k/o mice associated with asthma-like

symptoms and inflammatory diseases. However, the specification fails to provide guidance to correlate the increased ratio of mature dendritic to immature dendritic cells in the k/o mice to the delivery of an active agent for inducing expression of RUNX3 in immune cells thereby reducing the proportion of mature DCs to immature DCs in the subject. For example, in pulmonary inflammatory diseases, the art teaches that a more detailed phenotypic analysis of dendritic cells in their role of inflammatory processes in the pathogenesis of pulmonary arterial hypertension (PAH) need to be performed (**Lambrecht et al,** Eur Respir J, 29: 435-437, 2007, (IDS)) p 436, 2nd column, last paragraph). The lack of significant effects of systemic steroids in idiopathic PAH patients provides an argument against the role of DCs in PAH (**Lambrecht,** p 436, 2nd column, last paragraph). **Lambrecht et al,** reports that the most important question even in 2007 is what the functional role of dendritic is cells in PAH (p 436, 1st column, 2nd paragraph). **Wallet et al,** (Clinical Medicine & Research, 3(3): 166-178, 2005, (IDS)) reports that the molecular targets of TGF-beta mediated suppression in DCs remain ill defined and one such target appears to be the RUNX3 transcription factor (p 170, 1st column, 2nd paragraph). **Wallet et al,** (Clinical Medicine & Research, 3(3): 166-175, 2005, (IDS)) indicates that primarily a contrasting role of DCs has been described as a function of maturation where immature DCs were largely considered to be non-inflammatory or tolerogenic, but mature dendritic cells were considered capable of eliciting a pro-inflammatory immune responses and although generally correct, this paradigm is now proving too simple (p 166, 1st column). This issue is further complicated by the identification of distinct subtypes of dendritic cells that exhibit different antigen-presenting cell effector functions (abstract).

As a third issue the claims embrace ex vivo stem cell generation overexpressing RUNX3 after delivery of an agent to immune cells for cell therapy in vivo. The specification as well as the art fails to provide guidance as such. Cell therapy in vivo after ex vivo growth of stem cells

is unpredictable as to the generation of stems cells after ex vivo culture manipulations of all types of immune cells from all species of a subject, route of administration of said cells in vivo and homing of functional stem cells to target tissues in vivo for effectively inhibiting T cell proliferation of target T cells in vivo or for reducing the ratio of mature to immature DCs in vivo. The use of autologous cells often implies an assumption of minimal manipulation and an inherent safety in the use of one's own cells. This is not entirely correct, as culture processes and reagents can alter cells, regardless of the origin (**Parenteau et al,** Ann. N.Y. Acad. Sci. 961: 27–39, 2002) (p 35 under issues of cell sourcing). **Blyth et al,** (Nature, 5: 376-387**,** 2005) while reviewing the status of RUNX genes note *RUNX3* is also associated with proliferation of mitogen-activated and Epstein–Barr virus (EBV)-immortalized primary B cells and seems to be required for the activated phenotype of these cells (p 383, 1st column, last paragraph). **Payne et al, (**Medical Hypotheses, 62: 718–720, 2004) note if stem cell therapy is to be maximally effective, it is vital that progenitor (stem) cells get to the target tissue(s) and/or organ(s) (abstract).

In light of the above, the state of the art is suggesting that that stem cell RUNX3 therapy in vivo after ex vivo generation of RUNX3 stem cells is unclear might be feasible in the future. The instant specification does not provide any relevant teachings, specific guidance, or working examples for overcoming the limitations of generating functional RUNX3 overexpessing stem cells ex vivo, administered by any route in vivo and homing to target tissues or cells resulting in inhibiting T cell proliferation of reducing the ratio of mature to immature DCs in vivo as raised by the art. Given the lack of guidance provided by the instant specification, it would have required undue experimentation to practice the invention as claimed for stem cell therapy in vivo resulting in inhibition of T cell proliferation or reducing the ration of mature to immature DCs in vivo in a subject by delivering said cells in vivo without a reasonable expectation of success.

Therefore, in view of the quantity of experimentation necessary to determine the parameters listed above for ex vivo delivering a agent to all types of immune cells, thereby inducing overexpression of RUNX3 stem cells, administering said cells in vivo, thereby inhibiting T cell proliferation in vivo, or reducing the ratio of mature to immature DCs in vivo, the lack of direction or guidance provided by the specification for ex vivo delivering a agent to all types of immune cells, thereby inducing overexpression of RUNX3 stem cells, administering said cells in vivo, thereby inhibiting T cell proliferation in vivo, or reducing the ratio of mature to immature DCs in vivo, the undeveloped state of the art pertaining to ex vivo delivering a agent to all types of immune cells, thereby inducing overexpression of RUNX3 stem cells, administering said cells in vivo, thereby inhibiting T cell proliferation in vivo, or reducing the ratio of mature to immature DCs in vivo,, and the breadth of the claims directed to all types of immune cells and agents, it would have required undue experimentation for one skilled in the art to make and/or use the claimed invention.

Applicants argue RUNX3 knock out mice exhibit higher levels of mature dendritic cells over immature dendritic cells, which, in turn, causes stimulation of T cell proliferation. Therefore, delivering an active agent comprising a polynucleotide encoding RUNX3 induces expression or overexpression of RUNX3 in the immune (dendritic) cells of the subject thereby inhibiting the proliferation of T cells and reducing the proportion of mature dendritic cells versus immature dendritic cells of the subject.

These arguments are not persuasive due to the unpredictability of ex vivo stem cell therapy and RUNX3 gene therapy. Applicant's failed to provide guidance as to how administration of stem cells in a subject expressing low or no levels of RUNX3 will result in inhibition T cell proliferation and reducing the proportion of mature to immature DCs in the subject. The art teaches if stem cell therapy is to be effective, it is vital that stem cells get to the

target tissue(s) and/or organ(s) (see above Payne et al). Applicants have not provided guidance as to what routes of administration of stem cells will get to the target T cells that will result in the inhibition of T cell proliferation and reduction of the proportion of mature to immature DCs. Applicants have not provided guidance as to what dose of stem cells will get to the target T cells that will result in the inhibition of T cell proliferation and reduction of the proportion of mature to immature DCs. The art teaches that cell therapy in vivo after ex vivo growth of stem cells is unpredictable as to the generation of stems cells after ex vivo culture manipulations of immune cells. For example, Parenteau teaches the use of autologous cells often implies an assumption of minimal manipulation and an inherent safety in the use of one's own cells however, this is not entirely correct, as culture processes and reagents can alter cells, regardless of the cell source. With regard to stem cell based RUNX3 gene therapy as embraced by the embodiments of the independent claims, which limit the agent to a polynucleotide encoding RUNX3 and RUNX3 promoter it is unpredictable if transduction of all types or what type of immune cells transduced with the RUNX3 in vitro will result in the production of stem cells due to the lack of RUNX3 known as an inducer of stem cell production far less as to whether those cells will inhibit T cell proliferation an reduce the proportion of mature to immature DCs in vivo.

Eventhough Applicants argue that RUNX3 knock out mice exhibit higher levels of mature DCs over immature DCs which in turn causes stimulation of T cell proliferation, however, as discussed above the art teaches the role of RUNX3 in cell proliferation is unclear (Coffman et al above). Coffman notes that independent studies from two different labs have demonstrated that *Runx3* knockout mice manifest severe limb ataxia due to defective development of proprioceptive neurons in the dorsal root ganglia while in another study *Runx3* knock out mice displayed hyperproliferation and suppressed apoptosis of epithelial cells in the gastric mucosa,

and died shortly after birth apparently due to starvation, however, this phenotype was not found in the *Runx3* knockout mice produced by Levanon et al and the reason for the discrepancy between the different *Runx3* knockout phenotypes is not clear. As such the art teaches that the role of RUNX3 in knock out mice is not clear even after the filing of the instant application.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 1 recites the limitation "stem cells" in line 6. There is insufficient antecedent basis for this limitation in the claim. There is no citation of stem cells, wherein the limitation is referred to.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Magdalene K. Sgagias whose telephone number is (571) 272-3305. The examiner can normally be reached on Monday through Friday from 9:00 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, Jr., can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

system, see http://pair-direct.uspto.gov. Should you have questions on access to private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

Magdalene K. Sgagias, Ph.D.
Art Unit 1632

/Anne-Marie Falk/
Anne-Marie Falk, Ph.D.
Primary Examiner, Art Unit 1632